II. REMARKS

A. Status of the Claims

Claims 37 and 38 were added. Support for claim 37 can be found, e.g., in paragraph [116] of the specification. Support for claim 38 can be found, e.g., in Table 1, Table 2 and Table 3 of the specification.

It is respectfully submitted that no new matter was added by virtue of the present amendments.

Claims 1-38 are pending.

B. Claim Rejections- 35 U.S.C. § 103

1. U.S. 2003/0229111 to Oshlack et al. in view of U.S. Patent No. 5,866,164 Kuczynski et al.

Claims 1-14, 17-19, 22, 27-36 were rejected under 35 U.S.C. § 103(a) over U.S. 2003/0229111 to Oshlack et al. in view of U.S. Patent No. 5,866,164 to Kuczynski et al.. The Examiner states on page 3 of the Office Action that because "Oshlack et al. teach dosage ranges of the compositions which fall within the ratios claimed, it would be desirable to optimize a dosage range between the two compositions to effectively treat pain."

The rejection is respectfully traversed.

The Manual of Patent Examining Procedure, section 2144.05, states:

> B. Only Result-Effective Variables Can Be Optimized
> A particular parameter must first be recognized as a result-effective variable, i.e., a variable which achieves a recognized result, before the

> determination of the optimum or workable ranges of said variable might be characterized as routine experimentation. *In re Antonie*, 559 F.2d 618, 195 USPQ 6 (CCPA 1977) (The claimed wastewater treatment device had a tank volume to contractor area of 0.12 gal./sq. ft. The prior art did not recognize that treatment capacity is a function of the tank volume to contractor ratio, and therefore the parameter optimized was not recognized in the art to be a result- effective variable.). See also *In re Boesch*, 617 F.2d 272, 205 USPQ 215 (CCPA 1980) (prior art suggested proportional balancing to achieve desired results in the formation of an alloy).

The Board of Patent Appeals and Interferences also holds the view that it is not obvious to optimize the parameter which "was not recognized in the prior art as one that would affect the results." *In re Whallen II, Appeal 2007-4423, July 23, 2008.* "Obviousness cannot be proven merely by showing that a known composition could have been modified by routine experimentation or solely on the expectation of success; it must be shown that those of ordinary skill in the art would have had some apparent reason to modify the known composition in a way that would result in the claimed composition." Id.

Applicants respectfully submit that the combination of the cited references does not provide a reason to a skilled person to modify the naltrexone to hydrocodone ratios exemplified in the Oshlack publication by lowering the naltrexone to hydrocodone ratio disclosed in the Oshlack publication to the specific ratios recited in the present claims, because the combination of the cited references does not teach or suggest what a result of such modification may be. Further, there is nothing in the cited reference that would support the conclusion that the purported "optimization" of the dosage forms described in the cited references would result in the claimed naltrexone to hydrocodone ratios.

The Oshlack publication is directed to stabilized naltrexone compositions. Applicants note that the naltrexone to hydrocodone ratios in the hydrocodone/naltrexone compositions described in the Oshlack publication are significantly higher than the ratios recited in the present claims.

Independent claims 1 and 22 recite, in part, that the ratio of naltrexone to hydrocodone in the claimed compositions is "from 0.011:1 to 0.0125:1."

Independent claim 27 recites, in part, that the ratio of naltrexone to hydrocodone in the claimed compositions is "0.0125:1."

The naltrexone to hydrocodone ratio in Example 22 of the Oshlack publication is 0.025:1, which is double the highest naltrexone to hydrocodone ratio recited in the present claims (i.e., 0.0125:1). The naltrexone to hydrocodone ratio of Example 20 of the cited reference is 0.1:1, which is eight times higher than the 0.0125:1 ratio recited in the present claims.

There is nothing in the cited references that indicates that the specific ratios recited in the present claims are desirable or beneficial, or that the ratios of naltrexone to hydrocodone in the dosage forms of the cited references may need to be adjusted. The combination of the cited references does not therefore provide a reason to the skilled person to alter the naltrexone to hydrocodone ratios exemplified in the Oshlack reference to the specific ratios recited in the present claims.

With further regard to claims 2-11 and 30-34, Applicants submit that the combination of the cited reference does not provide a reason for the skilled person to formulate a dosage form containing the relative amounts of naltrexone and hydrocodone recited in these claims. In fact, the Examiner acknowledges on page 5 of the Office Action that the Oshlack publication does not disclose the exact amounts of naltrexone and hydrocodone as recited in instant claims 2-11 and 30-34, and does not contend that the Kuczynski patent discloses these amounts. Accordingly, claims 2-11 are patentable over the combination of the cited references for this additional reason.

With further regard to claim 17, Applicants submit that the combination of the cited reference does not provide a reason to the skilled person to formulate a pharmaceutical composition, wherein hydrocodone and naltrexone are **substantially interdispersed** in a

sustained release excipient as recited in claim 17, because the Kuczynki patent describes dosage forms comprising opioid agonists and opioid antagonists in separate layers.

With further regard to claim 37, Applicants submit that the combination of the cited references does not teach or suggest an osmotic dosage form comprising a drug layer comprising both naltrexone and hydrocodone, as the Kuczynki patent, which has been relied upon by the Examiner for the teaching of osmotic dosage forms, describes osmotic dosage forms comprising opioid agonists and opioid antagonists in separate layers. Claim 37 is thus patentable over the combination of the cited references for this additional reason.

With further regard to claim 38, Applicants submit that there is no disclosure in the cited references of naltrexone hydrochloride dihydrate, and therefore claim 38 is not rendered obvious by the combination of the cited references for this additional reason.

For the foregoing reasons, and for the reasons presented in the previously filed responses, herein incorporated by reference, withdrawal of the rejection is respectfully requested.

2. U.S. 2003/0191147 to Sherman et al. in view of U.S. 2003/0031712 to Kaiko et al. and U.S. Patent No. 5,866,164 to Kuczynski et al.

Claims 1-36 were rejected over the combination of U.S. 2003/0191147 to Sherman et al., U.S. 2003/0031712 to Kaiko et al. and U.S. Patent No. 5,866,164 to Kuczynski et al..

The rejection is respectfully traversed.

Applicants respectfully submit that the combination of the cited references does not render the presently claimed naltrexone to hydrocodone ratios obvious, as the claimed ratios are not described by the cited references.

The combination of the cited reference also does not provide a reason for the skilled person to combine naltrexone and hydrocodone in the claimed ratios, as the combination of the cited references does not teach or suggest what a result of such modification may be.

Further, there is nothing in the cited reference that would support a conclusion that the purported "optimization" of the dosage forms described in the cited references would result in the claimed naltrexone to hydrocodone ratios.

Applicants respectfully submit that the ratio of naltrexone to hydrocodone in Example 15 of the Sherman publication (i.e., 0.01:1) is at least 10% lower than the lowest ratio recited in independent claims 1 and 22 (i.e., 0.011:1) and is 25% lower than the ratio recited in independent claim 27 (i.e., 0.125:1). Accordingly, Applicants submit that the ratio of naltrexone to hydrocodone in Example 15 of the Sherman publication does not meet the limitations of the naltrexone to hydrocodone ratios of independent claims 1, 22 and 27.

Applicants further submit that the naltrexone to hydrocodone ratio in Tables 1 and 2 of the Kaiko reference also does not meet the limitations of the naltrexone to hydrocodone ratios recited in independent claims 1, 22 and 27. In Tables 1 and 2 in the Kaiko reference, the weight ratio naltrexone per 1 mg of hydrocodone recited is "0.033 to 0.267," with a preferred ratio being "0.050 to 0.200." Applicants respectfully submit that this ratio is outside the ratio range recited in independent claims 1, 22 and 27, and is 2.6 times higher[1] than the 0.0125:1 ratio recited in claims 1, 22 and 27.

The Kuczynski patent also does not disclose the claimed nalrexone to hydrocodone ratio.

Therefore, the combination of the cited references does not describe the specific naltrexone to hydrocodone ratios recited in independent claims 1, 22 and 27, and therefore does not suggests the desirability of the claimed ratios or provide a reason for modification of the naltrexone to the hydrocodone ratios of the Sherman publication and the Kaiko publication.

[1] 0.033/0.0125=2.64.

With further regard to claims 2-11 and 30-34, Applicants submit that the combination of the cited reference does not provide a reason for the skilled person to formulate a dosage form containing the relative amounts of naltrexone and hydrocodone as recited in these claims. In fact, the Examiner acknowledges on page 7 of the Office Action that the Oshlack publication does not disclose the exact amounts of naltrexone and hydrocodone as recited in instant claims 2-11, and does not contend that the Kaiko publication or the Kuczynski patent disclose these amounts. Claims 2-11 are thus patentable over the combination of the cited references for this additional reason.

With further regard to claim 17, Applicants submit that the combination of the cited reference does not provide a reason to the skilled person to formulate a pharmaceutical composition, wherein hydrocodone and naltrexone are **substantially interdispersed** in a sustained release excipient as recited in claim 17, because the Kuczynki patent describes dosage forms comprising opioid agonists and opioid antagonists in separate layers.

With further regard to claim 37, Applicant submit that the combination of the cited references does not teach or suggest an osmotic dosage form comprising a drug layer comprising both naltrexone and hydrocodone as recited in claim 37, because the Kuczynski patent, which has been relied upon for the Examiner for the teaching of osmotic dosage forms, describes osmotic dosage forms comprising opioid agonists and opioid antagonists in separate layers. Claim 37 is therefore patentable over the combination of the cited references for this additional reason.

With further regard to claim 38, Applicants submit that there is no disclosure in the cited references of naltrexone hydrochloride dihydrate, and therefore claim 38 is not rendered obvious by the disclosure of the cited references for this additional reason.

For the foregoing reasons, and for the reasons presented in the previously filed responses, herein incorporated by reference, withdrawal of the rejection is respectfully requested.

III. Conclusion

An early and favorable action is earnestly solicited. According to currently recommended Patent Office policy, the Examiner is specifically authorized to contact the undersigned by telephone if the Examiner believes that a telephonic interview may advance the prosecution of the application.

Respectfully submitted,
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